Complete Summary

GUIDELINE TITLE

The role of gemcitabine in the treatment of cholangiocarcinoma and gallbladder cancer.

BIBLIOGRAPHIC SOURCE(S)

Dingle B, Rumble RB, Brouwers M, Gastrointestinal Cancer Disease Site Group. The role of gemcitabine in the treatment of cholangiocarcinoma and gallbladder cancer. Toronto (ON): Cancer Care Ontario (CCO); 2005 Apr 26. 16 p. (DQTC-SOS advice report; no. 1). [18 references]

GUIDELINE STATUS

This is the current release of the guideline.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Advanced or metastatic cancer of the gallbladder
- Cholangiocarcinoma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Technology Assessment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the role of gemcitabine in the treatment of cholangiocarcinoma and gallbladder cancer

TARGET POPULATION

Adult patients with advanced or metastatic cancer of the gallbladder, or with cholangiocarcinoma, for whom therapy with gemcitabine is being considered

INTERVENTIONS AND PRACTICES CONSIDERED

1. Monotherapy with gemcitabine
2. Combination therapy with gemcitabine with a fluoropyrimidine, such as 5-fluorouracil or capecitabine
3. Surgical resection

MAJOR OUTCOMES CONSIDERED

- Overall response rates
- Overall survival
- Adverse effects
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

The MEDLINE database was searched from 1996 to March (week 2) 2005. The following Medical subject headings (MeSH) "gemcitabine" and "gallbladder neoplasms" were combined, and results were limited to English only. In addition, conference proceedings from the 1998-2004 meetings of the American Society of Clinical Oncology were searched for abstracts of relevant trials, including the 2004 Gastrointestinal Cancers Symposium abstracts. The Canadian Medical Association

Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov/) were also searched for existing evidence-based practice guidelines. An additional article not found in the literature search, as it was too recent to be indexed, was obtained from a Gastrointestinal Cancer Disease Site Group (DSG) member.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from those sources were searched for additional trials.

Inclusion Criteria

Articles were selected for inclusion in the systematic review of the evidence if they were fully published English-language reports or published abstracts of:

1. Randomized controlled trials (RCTs) comparing gemcitabine, either alone or in combination, with best supportive care or other therapy in the treatment of cholangiocarcinoma or gallbladder cancer.
2. Phase II trials reporting on the efficacy or adverse effects detected in treatment with gemcitabine, alone or in combination, in the treatment of cholangiocarcinoma or gallbladder cancer.

Exclusion Criteria

1. Letters and editorials were not eligible.

NUMBER OF SOURCE DOCUMENTS

Thirteen single-arm phase II studies were obtained.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

As none of the trials obtained were randomized controlled trials (RCTs), no pooling of outcome data was possible.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This advice report, produced by the Program in Evidence-Based Care's (PEBC's) Gastrointestinal Cancer Disease Site Group (DSG), is a convenient and up-to-date source of the best available evidence on the role of gemcitabine in the treatment of gallbladder cancer developed through systematic reviews of the available evidence.

The most effective treatment for cancer of the gallbladder is surgical resection of the primary tumour along with any local spread, but surgery is dependent upon the patient presenting at an earlier, resectable stage. Curative resection of cholangiocarcinoma is more complex and is dependent on the site and extent of the tumour. Five-year survival after the surgical resection of stage I gallbladder cancer should be greater than 85%, but drops to 25%, 10%, and 2% for stage II, III, and IV tumours. For patients with resectable cholangiocarcinoma, five-year survival rates range from 35% to 45%. There is no generally accepted standard chemotherapy for advanced, non-resectable, cancer of the gallbladder or biliary tree. In advanced disease, median survival with best supportive care is approximately six months, and five-year survival rates approach 0%. In past phase II studies, response rates for the use of fluoropyrimidines in this population ranged from 10% to 28%.

Gemcitabine either alone or in combination with other commonly used drugs such as fluoropyrimidines or cisplatin has shown positive activity and response in phase II trials for the treatment of advanced biliary cancer. Single studies of gemcitabine in combination with oxaliplatin and carboplatin also suggest a similar response.

Considering the low incidence rate of these types of tumours and the poor performance status of many patients presenting with biliary cancer, conducting large trials to establish a standard of care is unlikely. Indeed, a search of the National Cancer Institute's Internet clinical trials database (http://www.cancer.gov/search/clinical_trials/) on March 23, 2005 for reports of new or ongoing trials revealed only two small Phase II trials (Appendix 3 in the original guideline document). Information on a third phase II trial (SAKK-44/02) was submitted by an Ontario clinician. Therefore, treatment decisions must be based on the balance of predictable toxicities and benefits. While none of the studies included in this systematic review measured and evaluated quality-of-life scores, the assumption that some benefit may accrue from complete and partial responses, if not also from stabilization of the disease, seems reasonable. Certainly the extension of median survival to over one year in some studies compares favourably with best supportive care by as much as six months.

Therefore, administering a trial of gemcitabine in selected patients, either as a single agent, or in combination with other drugs that have demonstrated a response in this treatment population, seems reasonable. In general, fluoropyrimidines have a more favourable toxicity profile compared with the alkylating platinum compounds (cisplatin, oxaliplatin, and carboplatin). Considering the improved response rates and survival in combination therapy, the use of gemcitabine and a fluoropyrimidine appears to be favoured. A recent article stated that a previous retrospective review of gemcitabine and continuous infusion 5-fluorouracil (5-FU) showed a similar benefit in terms of response but with

increased line-related infections and thromboembolitic complications, which suggests that when gemcitabine is given with a fluoropyrimidine, the fluoropyrimidine of choice should be capecitabine.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

See Appendix 1 in the original guideline document for recommended regimens and dosages.

- In appropriate patients with gallbladder cancer or cholangiocarcinoma, surgical resection offers the best chance for survival and should be the first treatment of choice.
- For patients who are not considered candidates for surgery with curative intent, but who are willing and able to tolerate treatment with chemotherapy, considering the lack of an effective standard treatment option, gemcitabine, either alone or in combination with a fluoropyrimidine such as 5-fluorouracil (5-FU) or capecitabine, is a reasonable alternative to best supportive care, although this conclusion has not been confirmed with a randomized controlled trial.
- Patients should be encouraged to enroll in randomized controlled trials comparing promising new treatments, such as gemcitabine in combination with a fluoropyrimidine against other treatments with proven response.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by single-arm phase II studies.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Five-year survival rates after surgical resection of stage I gallbladder cancer may be greater than 85%, but drops to 25%, 10%, and 2% for stage II, III, and IV tumours. For patients with non-resectable disease who are offered palliative chemotherapy only, the five-year survival rate approaches 0%.
- Gemcitabine either alone, or in combination with fluoropyrimidines, cisplatin, oxaliplatin, or carboplatin has shown positive activity and response in phase II trials treating advanced biliary cancer. Given the more favourable toxicity profile of fluoropyrimidines (either 5-fluorouracil/leucovorin or capecitabine) compared with the alkylating platinum compounds cisplatin, oxaliplatin, or carboplatin, and the apparent improved response rates and survival in combination therapy, the use of gemcitabine and a fluoropyrimidine is favoured.
- The expert opinion of the Gastrointestinal Cancer Disease Site Group is that some benefit may accrue from complete and partial responses, if not also from stabilization of the disease. In some of the phase II trials reviewed, the extension of median survival to over one year exceeds current results with best supportive care by as much as six months.

POTENTIAL HARMS

- Adverse effects observed in the trials of gemcitabine monotherapy are described as follows: one trial reported no grade 3-4 adverse effects, and one trial reported no grade 4 adverse effects. Two trials reported either grade 3 or grade 4 neutropenia. At least one trial reported the following grade 3-4 effects: anemia, nausea, flu-like symptoms, hemolytic uremic syndrome, and anorexia. Generally, the gemcitabine monotherapy trials reported that any adverse effects observed were mild and manageable. See Appendix 2 in the original guideline document for details of the observed adverse effects by trial.
- A variety of grade 3-4 adverse effects were observed in the trials of gemcitabine in combination with other drugs. The three trials investigating gemcitabine in combination with cisplatin reported granulocytopenia, thrombocytopenia, fever, asthenia, anorexia, neutropenia, anemia, and leukopenia. The trial investigating gemcitabine in combination with docetaxel reported alopecia, nausea/vomiting, mucositis, leukopenia, thrombocytopenia, and anemia. The trial investigating gemcitabine in combination with 5-fluorouracil/leucovorin (5-FU/LV) reported dyspnea, nausea/vomiting, fatigue, thrombocytopenia, diarrhea, infection, leukopenia, anemia, and elevation of liver enzymes. The trial investigating gemcitabine in combination with oxaliplatin reported neutropenia, thrombocytopenia, nausea/vomiting, and peripheral neuropathy. The trial investigating gemcitabine in combination with mitomycin-C reported leukopenia and thrombocytopenia. The trial investigating gemcitabine in combination with carboplatin reported nausea/vomiting, elevation of liver enzymes, proteinuria, hematuria, edema, and fatigue. The trial investigating gemcitabine in combination with capecitabine reported neutropenia (one case of febrile

neutropenia), thrombocytopenia, hand-foot rash, infection, fatigue, and thromboembolitis. See Appendix 2 in the original guideline document for details of the observed adverse effects by trial.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2005 Apr 26

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Gastrointestinal Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The members of the Program in Evidence-based Care (PEBC) Gastrointestinal Cancer Disease Site Group (DSG) declared that there were no potential conflicts of interest related to the topic of this Drug Quality Therapeutic Committee's Standing Oncology Subcommittee (DQTC-SOS) advice report.

GUIDELINE STATUS

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Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The role of gemcitabine in the treatment of cholangiocarcinoma and gallbladder cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2005 Apr 26. Various p. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on October 26, 2006. The information was verified by the guideline developer on November 24, 2006.

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